Table 6-1: Whole Blood Everolimus Pharmacokinetic Parameters in Patients Following XIENCE V Stent Implantation

	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t}[a] (ng.h mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
SPIRIT III RCT and 4.0 Arm							
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=3[b])	88 µg	0.050 (0.50-1.88)	0.3867 ± 0.09866		5.31 ± 4.114		
3.5-4.0 x 28 mm (n=6[c])	181 µg	0.50 (0.07-1.00)	1.175 ± 0.6817	79.08 ± 57.24	23.73 ± 13.63	44.00 ± 28.67	5.130 ± 2.114
SPIRIT III Japanese Arm							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=6)	88 µg	1.00 (0.50-1.02)	0.5017 ± 0.1398	45.22 ± 35.08	5.049 ± 2.138	12.98 ± 7.078	9.286 ± 6.069
3.5-4.0 x 18 mm (n=4[b])	113 µg	0.51 (0.50-0.53)	0.6500 ± 0.08756	53.57 ± 19.34	11.02 ± 4.002	19.97 ± 7.890	6.471 ± 2.807
SPIRIT II Clinical Trial							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{last} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=13)	88 µg	0.50 (0.13-2.17)	0.4369 ± 0.1507	54.08 ± 35.78	8.255 ± 5.863	19.60 ± 15.30	8.066 ± 6.443
3.5-4.0 x 18 mm (n=4[c])	113 µg	0.50 (0.50-0.50)	0.5850 ± 0.2630	47.60 ± 62.13	42.54 ± 58.83	22.79 ± 31.47	16.96 ± 13.07
3.5-4.0 x 28 mm (n=4)	181 µg	0.46 (0.17-1.00)	0.7925 ± 0.1406	103.4 ± 64.17	28.07 ± 13.18	52.71 ± 27.40	5.332 ± 5.048

[a] Accurate determination not possible due to rapid disappearance of everolimus from the blood
[b] n= 5 for $t_{1/2}$ and CL
[c] n= 3 for $t_{1/2}$ and CL
t_{max}(h)= time to maximum concentration
C_{max}= maximum observed blood concentration
$t_{1/2}$ (h)= terminal phase half-life
AUC_{0-t} or AUC_{last} = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
$AUC_{(0-\infty)}$= the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL= total blood clearance

In all subjects, the maximum time to everolimus disappearance was 168 hours; however, 1 subject in the SPIRIT II clinical trial had detectable levels at 30 days. In all 3 studies, the C_{max} value never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection. The PK parameters representing elimination; $t_{½}$, AUC_{0-t}, AUC_{last}, $AUC_{0-\infty}$, and CL could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents.

Everolimus disappearance from circulation following XIENCE V stent implantation should further limit systemic exposure and adverse events associated with long-term systemic administration at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies.

6.3 Interactions with Drugs or Other Substances

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the countertransporter P-glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods[3] listed below. Medications that are strong inhibitors of CYP3A4 might reduce everolimus metabolism *in vivo*. Hence, co-administration of strong inhibitors of CYP3A4 may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavor, erythromycin, clarithromycin, fluconazole, calcium channel blockers)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepin, phenobarbital, phenytoin)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit juice

6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of XIENCE V stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group (XIENCE V stent). The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group. Based on the results of this study, the XIENCE V stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

Genotoxicity studies were conducted on the XIENCE V stent in mammalian cells and bacteria. These studies included gene mutations in bacteria (Ames Test), gene mutations in mammalian cells (chromosomal aberration), test for clastogenicity in mammalian cells, and mammalian erythrocyte micronucleus test. Based on the results of these studies, the XIENCE V stent is not genotoxic.

[3] Certican® Investigator's Brochure. Novartis Pharmaceutical Corporation

In addition, a reproductive toxicity (teratology) study was conducted to demonstrate that implantation of XIENCE V stents in female Sprague-Dawley rats does not affect their fertility or reproductive capability and shows a lack of any reproductive toxicity on their offspring. The XIENCE V stent did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article (XIENCE V stent) and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of in utero mortality. Additionally, the XIENCE V stent did not cause any reproductive toxicity in the offspring in this study.

6.5 Pregnancy

Pregnancy Category C: There are no adequate everolimus or XIENCE V stent related studies in pregnant women. Effects of the XIENCE V stent on prenatal and postnatal rat development were no different than the controls. When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.

Effective contraception should be initiated before implanting a XIENCE V stent and continued for one year post-implantation. The XIENCE V stent should be used in pregnant women only if potential benefits justify potential risks.

Safety of the XIENCE V stent has not been evaluated in males intending to father children.

6.6 Lactation

It is unknown whether everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to XIENCE V stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

7.0 OVERVIEW OF CLINICAL STUDIES

Principal XIENCE V safety and effectiveness information is derived from the SPIRIT III clinical trial and is supported by the SPIRIT FIRST and SPIRIT II clinical trials. These studies evaluated XIENCE V EECSS performance in subjects with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and listed in Table 7-1.

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS^{2}™ Paclitaxel Eluting Coronary Stent System (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consisted of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Enrollment is complete in the RCT and the Japan arm.

The SPIRIT III RCT was a prospective, randomized (2:1; XIENCE V:TAXUS), active-controlled, single-blinded, multi-center, clinical trial in the US designed to evaluate the safety and efficacy

of the XIENCE V stent in the treatment of up to two *de novo* lesions • •28 mm in length in native coronary arteries with RVD • •2.5 mm to • •3.75 mm. The RCT study was designed to enroll 1,002 subjects at up to 80 sites in the US. The primary endpoint in the RCT was in-segment late loss at 240 days, and the co-primary endpoint was ischemia-driven target vessel failure (TVF, defined as the composite of cardiac death, MI, or clinically-driven TVR) at 270 days. Other secondary endpoints included clinical outcomes of all the subjects (30, 180, 270 days and annually from 1 to 5 years), as well as angiographic results and intravascular ultrasound (IVUS) results at 240 days. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III 4.0 mm arm was a prospective, multi-center, single-arm registry designed to evaluate the XIENCE V stent in the treatment of up to two *de novo* lesions • •28 mm in length in native coronary arteries with RVD > 3.75 mm to • •4.25 mm. This study was designed to enroll up to 80 subjects at up to 80 sites in the US. Enrolled subjects were scheduled for clinical follow-up at 30, 180, 240, and 270 days and annually from 1 to 5 years, with angiographic follow-up at 240 days. The primary endpoint was in-segment late loss at 240 days compared to the TAXUS arm from the SPIRIT III RCT. Follow-up through 1 year is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subset derived from the RCT[4] and Japan non-randomized arm. Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan).

The SPIRIT II clinical trial was a randomized, single-blind, active-control, multi-center clinical evaluation. Subject eligibility criteria were similar to the SPIRIT III clinical trial and enrollment duration overlapped between studies. In this study, 300 subjects (3:1 randomization XIENCE V: TAXUS) were enrolled at 28 sites outside the United States. The primary endpoint was in-stent late loss at 6 months. Secondary endpoints included clinical outcomes at 30, 180, 270 days and annually from 1 to 5 years; angiographic results at 180 days and 2 years; and IVUS results at 180 days and 2 years. Clinical follow-up through 2 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT FIRST clinical trial was a randomized, single-blind, controlled, multi-center first-in-man study. This trial was the first human study to evaluate the XIENCE V stent safety and performance. Sixty subjects [XIENCE V stent (n=28) and MULTI-LINK VISION bare metal control stent (n=32)] were enrolled at 9 sites in Europe. The primary endpoint was in-stent late loss at 6 months on the per-treatment evaluable population, and the major secondary endpoint was the percent in-stent volume obstruction (% VO) at 6 months based on IVUS analysis of the per-treatment evaluable population. Follow-up through 3 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

Table 7-1 summarizes the clinical trial designs for the SPIRIT family of trials.

[4] Includes one subject from the 4.0 mm non-randomized arm

Table 7-1: XIENCE V SPIRIT Clinical Trial Designs

	SPIRIT III clinical trial		SPIRIT II clinical trial	SPIRIT FIRST clinical trial
	RCT	Registries		
Study Type/Design	• Multi-center • Randomized • Single-blinded • Active-Control	• Multi-center • Single-arm • Open-label	• Multi-center • Randomized • Single-blinded • Active-Control	• Multi-center • Randomized • Single-blinded • Control
Number of Subjects Enrolled	Total: 1,002 XIENCE V: 668 TAXUS Control: 334	Total: 168 4.0 mm: 80 Japan: 88*	Total: 300 XIENCE V: 225 TAXUS Control: 75	Total: 60 XIENCE V: 30 VISION Control: 30
Treatment	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Single *de novo* lesion
Lesion Size	RVD: 2.5 - 3.75 mm Length: ≤ 28 mm	4.0 mm RVD: > 3.75 - 4.25 mm Length: ≤ 28 mm	RVD: 2.5 - 4.25 mm Length: ≤ 28 mm	RVD: 3 mm Length: ≤ 12 mm
		Japan RVD: 2.5 - 4.25 mm Length: ≤ 28 mm		
Stent Sizes (XIENCE V)	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 18, 28 mm	4.0 mm Diameter: 4.0 mm Length: 8, 18, 28 mm Japan Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 3.0 mm Length: 18 mm
Post-procedure Antiplatelet Therapy	Clopidogrel 6 months minimum (or ticlopidine per site standard), Aspirin 5 years	4.0 mm: same as RCT Japan: Ticlopidine 3 months, Aspirin 5 years	Clopidogrel 6 months minimum (or ticlopidine per site standard), Aspirin 1 year	Clopidogrel 3 months minimum (or ticlopidine per site standard), Aspirin 1 year
Primary Endpoint	In-segment late loss at 240-days	In-segment late loss at 240-days	In-stent late loss at 180-days	In-stent late loss at 180-days
Co-Primary Endpoint	TVF at 270-days	None	None	None
Clinical Follow-up	30, 180, 240, 270 days, 1 to 5 years	30, 180, 240, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years
Angiographic Follow-up	240 days (N=564)	240 days (All registry)	180-day (all), 2-years (N=152)	180-days, 1-year (all)
IVUS Follow-up	240 days (N=240)	240 days (Japan only)	180-day, 2-years (N=152)	180-days, 1-year (all)
PK Study	US: Minimum 15 subjects with single lesion, maximum 20 with dual lesions Japan: Minimum 10 subjects with single lesion, maximum 20 with dual lesions		Minimum 15 subjects with single lesion, maximum 20 with dual lesions	None
Status	One year reported; 2, 3, 4 and 5 years planned		One and 2 years reported; 3, 4 and 5 years planned	One, 2, and 3 years reported; 4 and 5 years planned

*Only pharmacokinetic substudy results included (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent).

8.0 ADVERSE EVENTS

8.1 Observed Adverse Events

Principal adverse event information is derived from SPIRIT III, SPIRIT II and SPIRIT FIRST clinical trials and is shown in Table 8.1-1 and 8.1-2. Within these tables, the Intent-to-Treat population includes all subjects randomized, while the Per-Treatment Evaluable population includes only those subjects who received a study device at the target lesion with no major procedure protocol deviations except deviations relating to the treatment arm, for whom follow-up data are available. See also Section 8.3 – Adverse Events, Potential Adverse Events. See Section 9.0 – Clinical Studies for more complete study design descriptions and results.

Table 8.1-1: SPIRIT III, II and FIRST:
Principal Adverse Events From Post-Procedure to 1 Year

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
In Hospital							
TVF[1]	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)
MACE[2]	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)
All Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Non-Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
QMI	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
NQMI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
Cardiac Death or MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
Ischemia-Driven Revascularization	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)
Ischemia-Driven TLR	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)
Ischemia-Driven Non-TLR TVR	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Stent Thrombosis[3] (Per Protocol)	0.3% (2/669)	0.0% (0/330)	1.4% (1/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
9 Months[4]							
TVF[1]	7.6% (50/657)	9.7% (31/320)	5.9% (4/68)	4.5 (10/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
MACE[2]	5.0% (33/657)	8.8% (28/320)	5.9% (4/68)	2.7% (6/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
All Death	1.1% (7/658)	0.9% (3/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.6% (4/658)	0.6% (2/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.3% (15/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
QMI	0.2% (1/657)	0.0% (0/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.1% (14/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Ischemia-Driven Revascularization	5.3% (35/657)	6.6% (21/320)	1.5% (1/68)	3.6% (8/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	1.5% (1/68)	1.8% (4/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TVR, non TLR TVR	2.9% (19/657)	4.1% (13/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis[3]							
Protocol	0.6% (4/654)	0.0% (0/319)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
1 Year[5]							
TVF[1]	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	4.5% (10/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
MACE[2]	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	2.7% (6/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	3.6% (8/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	1.8% (4/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven non-TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis[3]							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.0% (0/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)

Notes:
- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s)/lesion(s) for subjects with two target vessels / lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- SPIRIT II and III based on Intent to Treat Population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population [a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm (randomized versus actually received)].
- Revascularization includes TLR and Non-TLR TVR.
- Q wave MI for all SPIRIT Trials is defined as the development of new pathological Q wave on the ECG.
- Non Q wave MI for SPIRIT III is defined as the elevation of CK levels to greater than or equal to 2 times the upper limit of normal with elevated CKMB in the absence of new pathological Q waves.
- Non Q wave MI for SPIRIT II is defined as a typical rise and fall of CKMB with at least one of the following: Ischemia symptoms, ECG changes indicative of ischemia (ST segment elevation or depression), or coronary artery intervention.
  - If non procedural/spontaneous MI, CKMB is greater than or equal to 2 times upper limit of normal
  - If post PCI, CKMB is greater than or equal to 3 times upper limit of normal
  - If post CABG, CKMB is greater than or equal to 5 times upper limit of normal
- Non Q wave MI for SPIRIT FIRST is defined (WHO definition) as the elevation of post procedure CK levels to greater than or equal to 2 times the upper normal limit with elevated CKMB in the absence of new pathological Q waves.
- Non Q wave MI for SPIRIT FIRST is defined (ESC/ACC definition) as for non procedural, CKMB elevation greater than or equal to 2 times the upper normal limit, for post PCI, CKMB elevation greater than or equal to three times the upper normal limit, and for post CBAG, CKMB elevation greater than or equal to five times the upper normal limit.

[1] TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.
[2] MACE includes cardiac death, MI and ischemia-driven TLR.
[3] See Section 8.2 – Stent Thrombosis Definitions.
[4] SPIRIT III and SPIRIT FIRST includes 14 day window. SPIRIT III includes 9 month events identified at the 1 year follow-up.
[5] SPIRIT III and SPIRIT FIRST includes 28 day window.

Table 8.1-2: SPIRIT III, II and FIRST: Principal Adverse Events from Latest Follow-up

	SPIRIT III 1 Year[4]			SPIRIT II 2 Year[4]		SPIRIT FIRST 3 Year[4]	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
TVF[1]	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	10.0% (21/211)	12.3% (9/73)	15.4% (4/26)	32.1% (9/28)
MACE[2]	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	6.6% (14/211)	11.0% (8/73)	15.4% (4/26)	25.0% (7/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	3.7% (8/218)	6.5% (5/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.5% (1/218)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non-Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	3.2% (7/218)	5.2% (4/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/211)	0.0% (0/73)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	3.3% (7/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	7.1% (15/211)	9.6% (7/73)	7.7% (2/26)	32.1% (9/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	3.8% (8/211)	6.8% (5/73)	7.7% (2/26)	25.0% (7/28)
Ischemia-Driven non-TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	3.8% (8/211)	4.1% (3/73)	0.0% (0/26)	10.7% (3/28)
Stent Thrombosis[3]							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	1.9% (4/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.9% (2/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)

Notes:

- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s)/lesion(s) for subjects with two target vessels / lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- SPIRIT II and III based on Intent to Treat Population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population [a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm (randomized versus actually received)].
- Revascularization includes TLR and Non-TLR TVR.

[1] TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.
[2] MACE includes cardiac death, MI and ischemia-driven TLR.
[3] See Section 8.2 – Stent Thrombosis Definitions.
[4] SPIRIT III, SPIRIT II and SPIRIT FIRST includes 28 day window.

8.2 Stent Thrombosis Definitions

Protocol defined stent thrombosis (ST) was categorized as acute (< 1 day), subacute (1 - 30 days) and late (> 30 days) and was defined as any of the following[5]:

- Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (angiographic appearance of thrombus within or adjacent to a previously treated target lesion)
- In the absence of angiography, any unexplained death, or acute MI (ST segment elevation or new Q-wave)[6] in the distribution of the target lesion within 30 days

All stent thrombosis events were also classified using the ST definitions proposed by the Academic Research Consortium (ARC)[7]. This was performed by an independent event committee blinded to the treatment group of the individual subject. The committee categorized each incident of ST by timing and level of probability (definite, probable, possible), and relation to the original index procedure (primary, secondary after revascularization). These categories are defined as follows:

Timing:

- Early ST: 0 to 30 days post stent implantation
- Late ST: 31 days to 1 year post stent implantation
- Very late ST: > 1 year post stent implantation

Level of probability:

- Definite ST - considered to have occurred by either angiographic or pathologic confirmation
- Probable ST - considered to have occurred after intracoronary stenting in the following cases:
  1. Any unexplained death within the first 30 days.
  2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.
- Possible ST - considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up[8]

8.3 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedures including coronary stent use in native coronary arteries include, but are not limited to:

- Abrupt closure
- Access site pain, hematoma, or hemorrhage
- Acute myocardial infarction

[5] For SPIRIT FIRST Stent Thrombosis is defined as total occlusion by angiography at the stent site with abrupt onset of symptoms, elevated biochemical markers, and ECG changes consistent with MI.

[6] Non-specific ST/T changes, and cardiac enzyme elevations do not suffice.

[7] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circ* 2007;115:2344-51.

[8] All data within this Instructions for Use is presented as definite + probable only.

- Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
- Aneurysm
- Arterial perforation and injury to the coronary artery
- Arterial rupture
- Arteriovenous fistula
- Arrhythmias, atrial and ventricular
- Bleeding complications, which may require transfusion
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent embolism
- Coronary or stent thrombosis
- Death
- Dissection of the coronary artery
- Distal emboli (air, tissue or thrombotic)
- Emergent or non-emergent coronary artery bypass graft surgery
- Fever
- Hypotension and/or hypertension
- Infection and pain at insertion site
- Injury to the coronary artery
- Ischemia (myocardial)
- Myocardial infarction (MI)
- Nausea and vomiting
- Palpitations
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Renal failure
- Restenosis of the stented segment of the artery
- Shock/pulmonary edema
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of coronary artery
- Unstable or stable angina pectoris
- Vascular complications including at the entry site which may require vessel repair
- Vessel dissection

Adverse events associated with daily oral administration of everolimus to organ transplant patients include but are not limited to:

- Abdominal pain
- Acne
- Anemia
- Coagulopathy
- Diarrhea
- Edema
- Hemolysis
- Hypercholesterolemia
- Hyperlipidemia

- Hypertension
- Hypertriglyceridemia
- Hypogonadism male
- Infections: wound infection, urinary tract infection, pneumonia, pyelonephritis, sepsis and other viral, bacterial and fungal infections
- Leukopenia
- Liver function test abnormality
- Lymphocele
- Myalgia
- Nausea
- Pain
- Rash
- Renal tubular necrosis
- Surgical wound complication
- Thrombocytopenia
- Venous thromboembolism
- Vomiting

There may be other potential adverse events that are unforeseen at this time.

9.0 XIENCE V SPIRIT FAMILY OF CLINICAL TRIALS

9.1 SPIRIT III Pivotal Clinical Trial

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS^{2}™ Paclitaxel Eluting Coronary Stent System (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consists of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy. Enrollment is complete in the RCT and the Japan arm.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subject subset derived from the RCT[9] and Japan non-randomized arm (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan). Venous blood was drawn at regular intervals for pharmacokinetics analysis of total blood everolimus level at pre-determined sites.

9.1.1 SPIRIT III Randomized Clinical Trial (RCT)

Primary Objective: The objective of the SPIRIT III RCT was to demonstrate the non-inferiority in in-segment late loss at 240 days and target vessel failure at 270 days of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions • •28 mm in length in native coronary arteries with a reference vessel diameter (RVD) • •2.5 mm to • •3.75 mm. If non-inferiority of in-segment late loss was demonstrated, it was pre-specified that testing for superiority could be conducted.

[9] Includes one subject from the 4.0 mm non-randomized arm

Design: The SPIRIT III RCT was a prospective, 2:1 (XIENCE V:TAXUS) randomized, active-controlled, single-blinded, parallel, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions • •28 mm in length in native coronary arteries with RVD • •2.5 mm to • •3.75 mm. Given the available XIENCE V stent lengths of 8, 18 and 28 mm for this trial, in the XIENCE V arm, treatment of a target lesion > 22 mm and • •28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent. In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage. The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States.

All subjects had clinical follow-up at 30, 180, and 270 days and annually from 1 to 5 years. A pre-specified subgroup of 564 subjects had angiographic follow-up at 240 days. Of these 564, 240 subjects had IVUS at baseline and 240 days. Subjects that received a bailout stent also had IVUS at baseline and angiographic and IVUS follow-up at 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age was 63.2 years for the XIENCE V arm and 62.8 for the TAXUS arm. The XIENCE V had 70.1% (469/669) males and the TAXUS arm had 65.7% (218/332) males. The XIENCE V arm had 32.3% (215/666) of subjects with prior cardiac interventions and the TAXUS arm had 29.5% (98/332). The XIENCE V arm had 29.6% (198/669) of subjects with a history of diabetes and the TAXUS arm had 27.9% (92/330). The XIENCE V had 15.4% (103/669) of subjects with a lesion treated in two vessels and TAXUS had 15.4% (51/332). The XIENCE V arm had 8.1% (54/669) of subjects with planned stent overlap. The XIENCE V arm had 8.6% (57/666) of subjects with a history of prior CABG while the TAXUS arm had 3.6% (12/332) ($p = 0.0033$). The XIENCE V arm had 18.7% (123/657) of subjects with a history of unstable angina while the TAXUS arm had 25.1% (82/327) ($p=0.0243$). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.1.1-1 (Primary endpoints), Table 9.1.1-2 (Clinical Results), Table 9.1.1-3 (Angiographic and IVUS Results), Figure 9.1.1-1 (TVF Free Survival) and Table 9.1.1-4 (ARC-Defined Stent Thrombosis). These analyses are based on the intent to treat population.

The co-primary endpoint of in-segment late loss at 240 days was met with measurements of 0.14 ± 0.41 mm (301) for the XIENCE V arm and 0.28 ± 0.48 mm (134) for the TAXUS arm ($p < 0.0001$ for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-segment late loss at 240 days ($p = 0.0037$).

The co-primary endpoint of ischemia-driven TVF through 284 days was met with rates of 7.6% (50/657) for the XIENCE V arm and 9.7% (31/320) for the TAXUS arm ($p < 0.001$ for non-inferiority).

Table 9.1.1-1: SPIRIT III RCT Primary Endpoints Results

Measurements	XIENCE V (N=669) (M=376)	TAXUS (N=333) (M=188)	Difference [95% CI]	Non-Inferiority P-Value	Superiority P-Value
8 Month[1] Late Loss, In-segment (mm)	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	-0.14 [-0.23, -0.05][2]	<0.0001[3]	0.0037[4]
9 Month[5] Target Vessel Failure[6]	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%][2]	<0.0001[7]	Not Pre-specified

Notes:

•• N is the total number of subjects; M is the total number of analysis lesions.

•• One in SPIRIT III TAXUS arm subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

•• Analysis results include 9 month events identified at the 1 year follow-up.

[1] 8 month time frame includes follow-up window (240 + 28 days).

[2] By normal approximation.

[3] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.025 significance level.

[4] Two-sided p-value by superiority test using two-sample T-test, to be compared at a 0.05 significance level.

[5] 9 month time frame includes follow-up window (270 + 14 days).

[6] TVF is defined as hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[7] One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

Table 9.1.1-2: SPIRIT III RCT Clinical Results

	OUTCOMES AT 9 MONTHS			OUTCOMES AT 1 YEAR (latest available follow-up)		
	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]
COMPOSITE EFFICACY & SAFETY						
TVF[2]	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]	8.6% (56/653)	11.3% (36/320)	-2.67% [-6.75%, 1.40%]
MACE[3]	5.0% (33/657)	8.8% (28/320)[7]	-3.73% [-7.24%, -0.21%]	6.0% (39/653)	10.3% (33/320)	-4.34% [-8.14%, -0.54%]
EFFICACY						
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	-2.26% [-4.95%, 0.43%]	3.4% (22/653)	5.6% (18/320)	-2.26% [-5.13%, 0.62%]
TLR, CABG	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.0% (0/320)	0.31% [Assump. not met]
TLR, PCI	2.6% (17/657)	5.0% (16/320)	-2.41% [-5.09%, 0.27%]	3.1% (20/653)	5.6% (18/320)	-2.56% [-5.41%, 0.29%]
Ischemia-Driven non-TLR TVR	2.9% (19/657)	4.1% (13/320)	-1.17% [-3.68%, 1.34%]	3.1% (20/653)	4.4% (14/320)	-1.31% [-3.91%, 1.29%]
non-TLR TVR, CABG	0.5% (3/657)	0.6% (2/320)	-0.17% [Assump. not met]	0.6% (4/653)	0.6% (2/320)	-0.01% [Assump. not met]
non-TLR TVR, PCI	2.4% (16/657)	3.4% (11/320)	-1.00% [-3.32%, 1.32%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
SAFETY						
All Death	1.1% (7/658)	0.9% (3/321)	0.13% [Assump. not met]	1.2% (8/655)	1.2% (4/321)	-0.02% [Assump. not met]
Cardiac Death	0.6% (4/658)	0.6% (2/321)	-0.02% [Assump. not met]	0.8% (5/655)	0.9% (3/321)	-0.17% [Assump. not met]
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.14% [Assump. not met]	0.5% (3/655)	0.3% (1/321)	0.15% [Assump. not met]
MI	2.3% (15/657)	3.1% (10/320)	-0.84% [-3.06%, 1.38%]	2.8% (18/653)	4.1% (13/320)	-1.31% [-3.81%, 1.20%]
QMI	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.3% (1/320)	-0.01% [Assump. not met]
NQMI	2.1% (14/657)	3.1% (10/320)	-0.99% [-3.20%, 1.21%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	-0.86% [-3.30%, 1.59%]	3.4% (22/653)	4.7% (15/320)	-1.32% [-4.02%, 1.38%]
Stent Thrombosis – Protocol defined	0.6% (4/654)	0.0% (0/319)	0.61% [Assump. not met]	0.8% (5/647)	0.6% (2/317)	0.14% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (> 30 days)	0.2% (1/653)	0.0% (0/319)	0.15% [Assump. not met]	0.3% (2/646)	0.6% (2/317)	-0.32% [Assump. not met]

Notes:

** One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

** 9 month and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively.

** 9 months analysis results include 9 month events identified at the 1 year follow-up.

** Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.1.1-3: SPIRIT III 8 Month Angiographic and IVUS Results

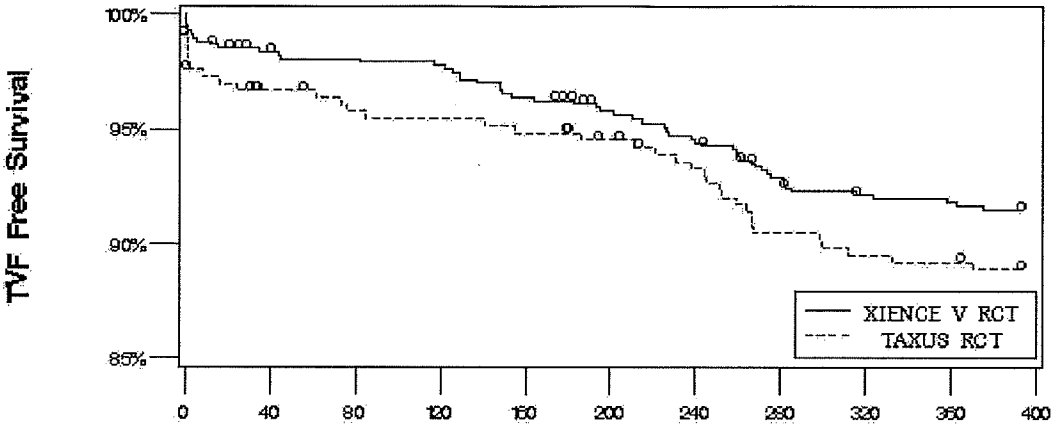
	XIENCE V (N=376) (M_{ANGIO}=427) (M_{IVUS}=181)	TAXUS (N=188) (M_{ANGIO}=220) (M_{IVUS}=93)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.71 ± 0.43 (425)	2.74 ± 0.40 (220)	-0.03 [-0.10, 0.04]
8 Months	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD			
Post-Procedure	2.35 ± 0.44 (426)	2.36 ± 0.45 (220)	-0.01 [-0.08, 0.06]
8 Months	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)	0.10 [-0.01, 0.21]
In-Stent %DS			
Post-Procedure	0.32 ± 8.86 (424)	-0.78 ± 10.65 (220)	1.10 [-0.55, 2.74]
8 Months	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-Segment %DS			
Post-Procedure	13.89 ± 8.04 (425)	13.92 ± 7.20 (220)	-0.03 [-1.26, 1.19]
8 Months	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
Late Loss			
In-Stent	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
In-Segment	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)	-0.13 [-0.21, -0.04]
Binary Restenosis			
In-Stent	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-Segment	4.7% (16/344)	8.9% (14/158)	-4.21% [-9.17%, 0.75%]
IVUS RESULTS			
Neointimal Volume (mm^3)	10.13 ± 11.46 (101)	20.87 ± 13.51 (41)	-10.74 [-20.92, -0.56]
% Volume Obstruction	6.91 ± 6.35 (98)	11.21 ± 9.86 (39)	-4.30 [-7.72, -0.88]
Incomplete Apposition			
Post Procedure	34.4% (31/90)	25.6% (11/43)	8.86% [-7.46%, 25.19%]
8 month	25.6% (23/90)	16.3% (7/43)	9.28% [-4.97%, 23.52%]
Persistent	24.4% (22/90)	14.0% (6/43)	10.49% [-3.15%, 24.13%]
Late Acquired	1.1% (1/90)	2.3% (1/43)	-1.21% [Assump. not met]

Notes:

- N is the total number of subjects; M_{ANGIO} is the total number of lesions in the protocol required angiographic cohort and M_{IVUS} is the total number of lesions in the protocol required IVUS cohort.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- 8 month time frame includes follow-up window (240 + 28 days).
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Figure 9.1.1-1: SPIRIT III: Survival Free of Target Vessel Failure through 1 Year



TVF	Event Free	Event Rate	P-value[1]
XIENCE V	91.5%	8.5%	0.18
TAXUS	88.9%	11.1%	

Note:
Time Frame includes follow-up window (365 + 28 days).
[1]P-value based on log rank and not adjusted for multiple comparisons

Table 9.1.1-4: SPIRIT III RCT ARC defined Definite+Probable Stent Thrombosis Through 1 Year

	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	1.1% (7/648)	0.6% (2/317)	0.45% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.4% (3/667)	0.0% (0/330)	0.45% [Assump. not met]
Late (> 30 days)	0.5% (3/647)	0.6% (2/317)	-0.17% [Assump. not met]

Notes:
** One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
** Time Frame includes follow-up window (365 + 28 days).
** Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.
[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.1.2 SPIRIT III US 4.0 mm Arm

Primary Objective: The objective of the SPIRIT III 4.0 mm arm was to demonstrate the non-inferiority in in-segment late loss at 240 days compared to the TAXUS arm of the SPIRIT III RCT.

Design: The SPIRIT III 4.0 mm study was a prospective, single-arm, multi-center clinical trial in the United States evaluating the 4.0 mm diameter XIENCE V stent. Sixty-nine (69) subjects were enrolled in the SPIRIT III 4.0 mm study arm.

All subjects had clinical follow-up at 30, 180, 240, and 270 days, and annually from 1 to 5 years. In addition, all subjects had angiographic follow-up at 240 days. IVUS was performed for subjects who received a bailout stent at baseline and 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age in the SPIRIT III 4.0 arm was 61.9 years with 72.5% (50/69) male, 21.7% (15/69) had prior cardiac interventions, and 30.4% (21/69) had a history of diabetes.

Results: The results are presented in Table 9.1.2-1 (Primary endpoints), Table 9.1.2-2 (Clinical Results), Table 9.1.2-3 (Angiographic Results), and Table 9.1.2-4 (ARC-Defined Stent Thrombosis). These analyses were performed on the intent to treat population.

The primary endpoint of in-segment late loss at 240 days was met with measurements of 0.17 ± 0.38 mm (49) for the XIENCE V 4.0 mm arm and 0.28 ± 0.48 mm (134) for the TAXUS arm from the SPIRIT III RCT ($p < 0.0001$ for non-inferiority).

Table 9.1.2-1: SPIRIT III 4.0 mm Primary Endpoints Results

Measurements	XIENCE V (M=69)	TAXUS (M=188)	Difference [95% CI]	Non-Inferiority P-Value
8 Month Late Loss, In-segment (mm)	0.17 ± 0.38 (49)	0.28 ± 0.48 (134)	-0.11 [-0.24, 0.03][1]	<0.0001[2]

Notes:
- M is the total number of analysis lesions.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time Frame includes follow-up window (240 + 28 days).

[1] By normal approximation.
[2] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.038 significance level.

Table 9.1.2-2: SPIRIT III 4.0 mm Clinical Results

	OUTCOMES AT 9 MONTHS XIENCE V (N=69)	OUTCOMES AT 1 YEAR (latest available follow-up) XIENCE V (N=69)
COMPOSITE EFFICACY & SAFETY		
TVF[1]	5.9% (4/68)	5.9% (4/68)
MACE[2]	5.9% (4/68)	5.9% (4/68)
EFFICACY		
Ischemia-Driven TLR	1.5% (1/68)	1.5% (1/68)
TLR, CABG	0.0% (0/68)	0.0% (0/68)
TLR, PCI	1.5% (1/68)	1.5% (1/68)
Ischemia-Driven non-TLR TVR	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, CABG	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, PCI	0.0% (0/68)	0.0% (0/68)
SAFETY		
All Death	1.5% (1/68)	1.5% (1/68)
Cardiac Death	1.5% (1/68)	1.5% (1/68)
Non-Cardiac Death	0.0% (0/68)	0.0% (0/68)
MI	4.4% (3/68)	4.4% (3/68)
QMI	0.0% (0/68)	0.0% (0/68)
NQMI	4.4% (3/68)	4.4% (3/68)
Cardiac Death or MI	5.9% (4/68)	5.9% (4/68)
Stent Thrombosis – Protocol defined	1.5% (1/67)	1.5% (1/67)
Acute (< 1 day)	1.4% (1/69)	1.4% (1/69)
Subacute (1 – 30 days)	0.0% (0/69)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)	0.0% (0/67)

Notes:

** 9 months and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively. 9 month analysis includes 9 month events identified at the 1 year follow-up.

[1] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[2] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.1.2-3: SPIRIT III 4.0 mm 8 Month Angiographic Results

	XIENCE V (N=69) (M=69)
ANGIOGRAPHIC RESULTS	
In-Stent MLD	
Post-Procedure	3.46 ± 0.38 (69)
8 Months	3.36 ± 0.46 (49)
In-Segment MLD	
Post-Procedure	3.07 ± 0.43 (69)
8 Months	2.91 ± 0.51 (49)
In-Stent %DS	
Post-Procedure	2.12 ± 10.27 (69)
8 Months	4.78 ± 13.20 (49)
In-Segment %DS	
Post-Procedure	13.42 ± 8.08 (69)
8 Months	17.92 ± 10.83 (49)
Late Loss	
In-Stent	0.12 ± 0.34 (49)
In-Segment	0.17 ± 0.38 (49)
Binary Restenosis	
In-Stent	0.0% (0/49)
In-Segment	2.0% (1/49)

Notes:
- N is the total number of subjects; M is the total number of lesions at baseline.
- 8 month time frame includes follow-up window (240 + 28 days).

Table 9.1.2-4: SPIRIT III 4.0 mm ARC defined Definite+Probable Stent Thrombosis Through 1 Year

	XIENCE V (N=69)
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	0.0% (0/67)
Acute (< 1 day)	0.0% (0/69)
Subacute (1 – 30 days)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)

Notes:
- Time Frame includes follow-up window (365 + 28 days).

9.2 SPIRIT II Supportive Clinical Trial

Primary Objective: The objective of the SPIRIT II clinical study was to demonstrate the non-inferiority in in-stent late loss at 180 days of the XIENCE V stent to the TAXUS stent in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. The SPIRIT II clinical study arm allowed the treatment of *de novo* lesions • •28 mm in length in coronary arteries with a reference vessel diameter (RVD) • •2.5 mm to • •4.25 mm. If non-inferiority of in-stent late loss was demonstrated, it was pre-specified that testing for superiority could be conducted. SPIRIT II was performed outside of the U.S.

Design: The SPIRIT II clinical study was a prospective, active-control, 3:1 (XIENCE V:TAXUS) randomized, single-blind, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions • •28 mm in length in native coronary arteries with RVD • •2.5 mm to • •4.25 mm. Given the available Xience V stent lengths of 8, 18 and 28 mm for this trial, in the Xience V arm, treatment of a target lesion > 22 mm and • •28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent. In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage.

Three hundred (300) subjects were enrolled in the study at 28 international sites in Europe, India and New Zealand.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiographic follow-up at 180 days with planned additional angiographic and IVUS follow-up at 2 years in a pre-specified subgroup of 152 consecutively enrolled subjects at selected sites.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

A subgroup of 39 subjects were enrolled in a pharmacokinetic (PK) substudy. Venous blood was drawn at regular intervals for PK analysis of total blood everolimus level at 7 pre-determined sites.

Demographics: The mean age was 62.0 years for the XIENCE V arm and 61.9 years for the TAXUS arm. The XIENCE V had 70.9% (158/223) males and the TAXUS arm had 79.2% (61/77) males. The XIENCE V arm had 23.3% (52/223) of subjects with prior cardiac interventions and the TAXUS arm had 22.1% (17/77). The XIENCE V arm had 22.9% (51/223) of subjects with a history of diabetes and the TAXUS arm had 23.7% (18/76). The XIENCE V had 16.6% (37/223) of subjects with a lesion treated in two vessels and TAXUS had 18.2% (14/77). The XIENCE V arm had 10.8% (24/223) of subjects with planned stent overlap. The XIENCE V arm had 18.4% (40/217) of subjects with a history of an MI within two months while the TAXUS arm had 7.8% (6/77) (p=0.0284). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.2-1 (Primary endpoint), Table 9.2-2 (Clinical Results), Table 9.2-3 (Angiographic and IVUS Results), and Table 9.2-4 (ARC-Defined Stent Thrombosis). These analyses were based on the intent to treat population.

The primary endpoint of in-stent late loss at 180 days was met with measurements of 0.11 ± 0.27 mm (201) for the XIENCE V arm and 0.36 ± 0.39 mm (73) for the TAXUS arm ($p < 0.0001$ for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-stent late loss at 180 days ($p < 0.0001$).

Table 9.2-1: SPIRIT II Primary Endpoint Result

Measurements	XIENCE V (N=223) (M=201)	TAXUS (N=77) (M=73)	Difference [95% CI]	Non-Inferiority P-Value	Superiority P-Value
180 Day Late Loss, In-stent (mm)	0.11 ± 0.27 (201)	0.36 ± 0.39 (73)	-0.24 [-0.34, -0.15][1]	<0.0001[2]	<0.0001[3]

Notes:
- N is the number of subjects and M is the total number of analysis lesions.

[1]By normal approximation.
[2]One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.16 mm, to be compared at a 0.0448 significance level.
[3]P-value from two-sided t-test.

Table 9.2-2: SPIRIT II Clinical Results

	OUTCOMES AT 6 MONTHS			OUTCOMES AT 2 YEARS (latest available follow-up)		
	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI][1]	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI][1]
COMPOSITE EFFICACY & SAFETY						
[illegible]	3.6% (8/222)	6.5% (5/77)	-2.89% [-8.92%, 3.14%]	10.0% (21/211)	12.3% (9/73)	-2.38% [-10.93%, 6.18%]
MACE[3]	2.7% (6/222)	6.5% (5/77)	-3.79% [-9.69%, 2.11%]	6.6% (14/211)	11.0% (8/73)	-4.32% [-12.24%, 3.59%]
EFFICACY						
[illegible]	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
[illegible]	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
[illegible]	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
Ischemia-Driven non-TLR TVR	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.8% (8/211)	4.1% (3/73)	-0.32% [Assump. not met]
[illegible]	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.5% (1/211)	0.0% (0/73)	0.47% [Assump. not met]
[illegible]	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.3% (7/211)	4.1% (3/73)	-0.79% [Assump. not met]
SAFETY						
All Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.7% (8/218)	6.5% (5/77)	-2.82% [-8.87%, 3.22]
Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	0.5% (1/218)	1.3% (1/77)	-0.84% [Assump. not met]
Non-Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.2% (7/218)	5.2% (4/77)	-1.98% [Assump. not met]
MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
QMI	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
NQMI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
Cardiac Death or MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	3.3% (7/211)	5.5% (4/73)	-2.16% [Assump. not met]
Stent Thrombosis – Protocol defined	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Late (> 30 days)	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]

Notes:

- •6 months and 2 year time frames include follow-up window (180 +14 days and 730 + 28 days).
- •Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.
[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.2-3: SPIRIT II 180-Day Angiographic and IVUS Results

	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.49 ± 0.40 (260)	2.62 ± 0.45 (91)	-0.13 [-0.24, -0.03]
6 Months	2.38 ± 0.50 (237)	2.27 ± 0.54 (86)	0.10 [-0.03, 0.23]
In-Segment MLD			
Post-Procedure	2.15 ± 0.44 (260)	2.22 ± 0.53 (91)	-0.07 [-0.19, 0.05]
6 Months	2.10 ± 0.51 (237)	2.08 ± 0.54 (86)	0.02 [-0.11, 0.15]
In-Stent %DS			
Post-Procedure	13.01 ± 6.02 (260)	12.66 ± 5.53 (91)	0.35 [-1.01, 1.71]
6 Months	15.70 ± 9.88 (237)	20.89 ± 11.59 (86)	-5.18 [-7.96, -2.41]
In-Segment %DS			
Post-Procedure	22.51 ± 8.98 (260)	23.36 ± 11.20 (91)	-0.86 [-3.43, 1.72]
6 Months	23.61 ± 11.65 (237)	27.05 ± 12.68 (86)	-3.44 [-6.53, -0.35]
Late Loss			
In-Stent	0.12 ± 0.29 (237)	0.37 ± 0.38 (86)	-0.25 [-0.34, -0.16]
In-Segment	0.07 ± 0.33 (237)	0.15 ± 0.38 (86)	-0.08 [-0.17, 0.01]
Binary Restenosis			
In-Stent	1.3% (3/237)	3.5% (3/86)	-2.22% [Assump. not met]
In-Segment	3.4% (8/237)	5.8% (5/86)	-2.44% [-7.89%, 3.02%]
IVUS RESULTS			
Neointimal Volume (mm^3)	3.83 ± 6.55 (99)	14.42 ± 16.03 (40)	-10.60 [-15.87, -5.32]
% Volume Obstruction	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	-4.85 [-7.27, -2.42]
Incomplete Apposition			
Post Procedure	6.5% (7/108)	5.6% (2/36)	0.93% [Assump. not met]
6 month	2.9% (3/103)	0.0% (0/39)	2.91% [Assump. not met]
Persistent	2.5% (3/120)	0.0% (0/42)	2.50% [Assump. not met]
Late Acquired	0.0% (0/104)	0.0% (0/39)	0.00% [Assump. not met]

Notes:
- N is the total number of subjects; M is the total number of lesions.
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Table 9.2-4: SPIRIT II ARC defined Definite+Probable Stent Thrombosis Through 2 Years

	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 2 years)	0.9% (2/211)	1.4% (1/73)	-0.42% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	1.3% (1/77)	-1.30% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/220)	1.3% (1/77)	-1.30% [Assump. not met]
Very Late (1 – 2 years)	0.9% (2/211)	0.0% (0/72)	0.95% [Assump. not met]

Note:
••Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.
[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.3 SPIRIT FIRST Randomized Clinical Trial

Objective: The objective of the SPIRIT FIRST randomized clinical trial was to assess the feasibility and performance of the XIENCE V stent (called VISION-E within the SPIRIT FIRST study) in the treatment of subjects with a single *de novo* native coronary artery lesion with reference vessel diameter (RVD) of 3.0 mm and lesion length ••12 mm. This study compared the XIENCE V stent to a matched uncoated metallic stent control (MULTI-LINK VISION).

Design: SPIRIT FIRST was a single-blind multi-center randomized controlled trial to assess the safety and performance of everolimus eluting from a durable polymer on a cobalt chromium stent (XIENCE V stent). Sixty (60) subjects were enrolled in the study.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiography and IVUS at baseline and at 180 days and 1 year follow-up.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 3 months and aspirin daily to be taken throughout the length of the trial (1 year).

Demographics: The mean age was 64.2 years for the XIENCE V arm and 61.4 years for the VISION arm. The XIENCE V had 70.4% (19/27) males and the VISION arm had 75.9% (22/29) males. The XIENCE V arm had 18.5% (5/27) subjects with prior cardiac interventions and the VISION arm had to 6.9% (2/29). The XIENCE V arm had 11.1% (3/27) subjects with a history of diabetes and the VISION arm had 10.3% (3/29). XIENCE V arm had 70.4% (19/27) of subjects with hypertension requiring medication while the VISION arm had 41.4% (12/29) (p=0.035). The remaining subject baseline clinical features were also well-matched between the XIENCE V arm and the VISION arm.

Results: The results are presented in Table 9.3-1 (Primary endpoint), Table 9.3-2 (Clinical Results), Table 9.3-3 (Angiographic and IVUS Results), and Table 9.3-4 (ARC-Defined Stent Thrombosis). These analyses were based on the per protocol evaluable population.

The primary superiority endpoint of in-stent late loss at 180 days was met with measurements of 0.10 ± 0.23 mm (23) for the XIENCE V arm and 0.85 ± 0.36 mm (27) for the MULTI-LINK VISION arm ($p < 0.0001$).

Table 9.3-1: SPIRIT FIRST Primary Endpoint Result

Measurements	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]	Superiority P-value [2]
180 Days Late Loss, In-stent (mm)	0.10± 0.23 (23)	0.85± 0.36 (27)	-0.76 [-0.93, -0.59] [1]	< 0.0001

Note: N is the number of subjects.
[1]By normal approximation
[2]One-tailed p-value by t-test, to be compared to a 5% significance level

Table 9.3-2: SPIRIT FIRST Clinical Results

	OUTCOMES AT 6 MONTHS[1]			OUTCOMES AT 3 YEARS[1] (latest available follow-up)		
	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][2]	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][2]
COMPOSITE EFFICACY & SAFETY						
TVF[3]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]]	15.4% (4/26)	32.1% (9/28)	-16.76% [Assump. not met]
MACE[4]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]	15.4% (4/26)	25.0% (7/28)	-9.62% [Assump. not met]
EFFICACY						
Ischemia-Driven TLR	3.8% (1/26)	21.4% (6/28)	-17.58% [Assump. not met]	7.7% (2/26)	25.0% (7/28)	-17.31% [Assump. not met]
TLR, CABG	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
TLR, PCI	3.8% (1/26)	17.9% (5/28)	-14.01% [Assump. not met]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]
Ischemia-Driven non-TLR TVR	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	10.7% (3/28)	-10.71% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
non-TLR TVR, PCI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	7.1% (2/28)	-7.14% [Assump. not met]
SAFETY						
All Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Non-Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
QMI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
NQMI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
Cardiac Death or MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
Stent Thrombosis – Protocol defined	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Late (> 30 days)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:
** Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.
[1] 6 month and 3 year time frames include follow-up window (180 +14 days and 1095 + 28 days) respectively.
[2] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.
[3] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[4] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.3-3: SPIRIT FIRST 180-Day Angiographic and IVUS Results

	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.34± 0.26 (27)	2.43± 0.30 (29)	-0.09 [-0.24, 0.06]
6 Months	2.28± 0.33 (23)	1.58± 0.41 (27)	0.70 [0.49,0.91]
In-Segment MLD			
Post-Procedure	2.07± 0.37 (27)	2.15± 0.37 (29)	-0.08 [-0.28, 0.12,]
6 Months	2.04 ± 0.40 (23)	1.54± 0.41 (27)	0.50 [0.27, 0.73]
In-Stent %DS			
Post-Procedure	12.34 ± 4.02 (27)	14.85 ± 4.76 (29)	-2.51 [-4.87, -0.16]
6 Months	15.57 ± 7.64 (23)	38.61 ± 14.25 (27)	-23.05 [-29.45, -16.64]
In-Segment %DS			
Post-Procedure	20.82 ± 7.65 (27)	23.14 ± 8.03% (29)	-2.32 [-6.52, 1.88]
6 Months	21.89 ± 11.15 (23)	40.78 ± 13.67 (27)	-18.89 [-25.95,-11.83]
Late Loss			
In-Stent	0.10 ± 0.23 (23)	0.85 ± 0.36 (27)	-0.76 [-0.93, -0.59]
In-Segment	0.09 ± 0.20 (23)	0.61 ± 0.37 (27)	-0.53 [-0.69, -0.36]
Binary Restenosis			
In-Stent	0.0% (0/23)	25.9% (7/27)	-25.93% [Assump. not met]
In-Segment	4.3% (1/23)	33.3% (9/27)	-28.99% [Assump. not met]
IVUS RESULTS			
Neointimal Volume (mm^3)	10.29± 13.32 (21)	38.29± 19.08 (24)	-28.00 [-37.82, -18.19]
% Volume Obstruction	7.95± 10.44 (21)	28.11± 13.98 (24)	-20.16 [-27.53, -12.79]
Incomplete Apposition			
Post Procedure	0.0% (0/ 27)	10.7% (3/ 28)	-10.71% [Assump. not met]
6 month	0.0% (0/ 21)	0.0% (0/ 22)	0.00% [Assump. not met]
Persistent	0.0% (0/ 27)	0.0% (0/ 28)	0.00% [Assump. not met]
Late Acquired	0.0% (0/ 21)	0.0% (0/ 22)	0.00% [Assump. not met]

Note:
[*] Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.
[1]Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Table 9.3-4: SPIRIT FIRST ARC defined Definite+Probable Stent Thrombosis Through 3 Years

	XIENCE V (N=27)	VISION (N=29)	Difference [95% CI]¹
ARC Definite+Probable Stent Thrombosis (0 days – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Very Late (1 – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:
** Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.
[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.4 SPIRIT II AND SPIRIT III POOLED ANALYSIS

In order to better estimate the incidence of low frequency events or outcomes in various specific subject subgroups, a subject-level pooled analysis was conducted of both randomized trials comparing the XIENCE V stent versus the TAXUS stent. Data from the SPIRIT II and SPIRIT III clinical trials were pooled to compare the XIENCE V stent to the TAXUS control stent in 1302 subjects out to 1 year (393 days) of follow-up. These two studies have subjects with similar baseline and angiographic characteristics and the key elements of study design including inclusion and exclusion criteria and endpoint definitions are comparable. The subject level data were included until the latest available time point of 1 year for each trial. Table 9.4-1 shows the subject disposition over time for the SPIRIT II and III RCT. The percentage of the total number of subjects that were enrolled in the studies and completed their 1 year follow-up was 96.5%.

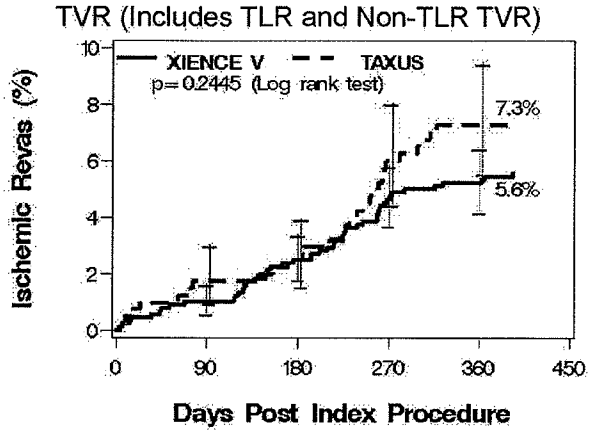
Table 9.4-1: Subject Disposition Table (N=1302; SPIRIT II and SPIRIT III RCT)

	30-Day Follow-up XIENCE V (890)		9-Month Follow-up XIENCE V (873)		1-Year Follow-up XIENCE V (866)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	223	667	220	653	220	646
	TAXUS (407)		TAXUS (395)		TAXUS (392)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	77	330	76	319	76	316

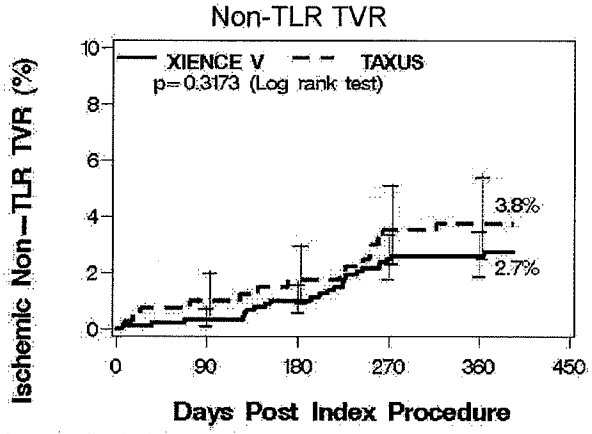
It is acknowledged that these retrospective pooled analyses are exploratory and hypothesis-generating. Definitive proof of the presence or absence of any differences between such sub-groups requires prospectively powered assessment in dedicated clinical trials. The pooled analysis from SPIRIT II and SPIRIT III trials includes subjects from single-blind trials with similar inclusion and exclusion criteria in 1,302 subjects with 1,506 lesions.

As shown in Figure 9.4-1, at one year, the analyses of pooled trials suggest a reduction in the rates of TVR and TLR for the XIENCE V stent compared to the TAXUS stent through one year. All CI bars represent a 1.5 standard error.

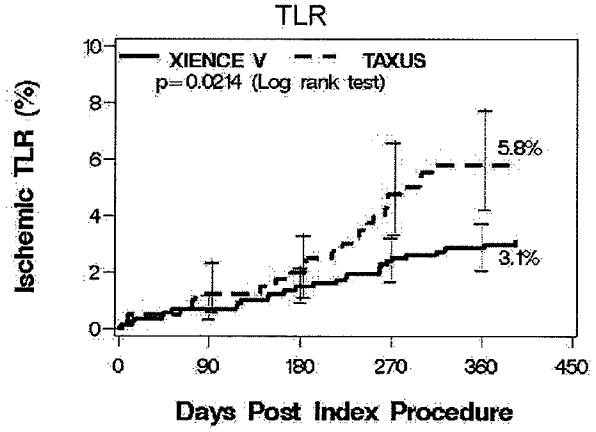
Figure 9.4-1: Kaplan Meier Hazard Curves for Time to First TVR or TLR Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



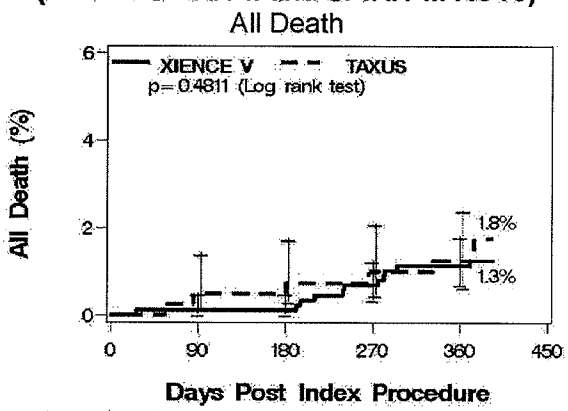
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



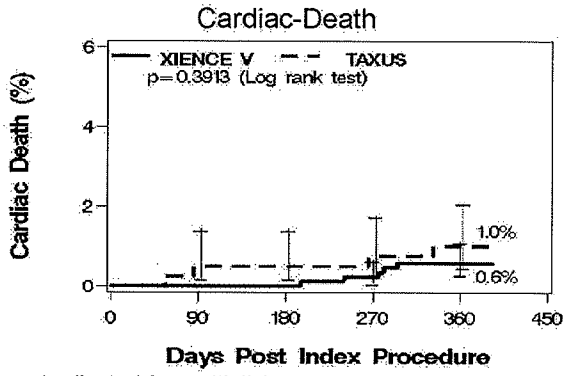
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of all death, cardiac death, and non-cardiac death through 1 year are shown in Figure 9.4-2.

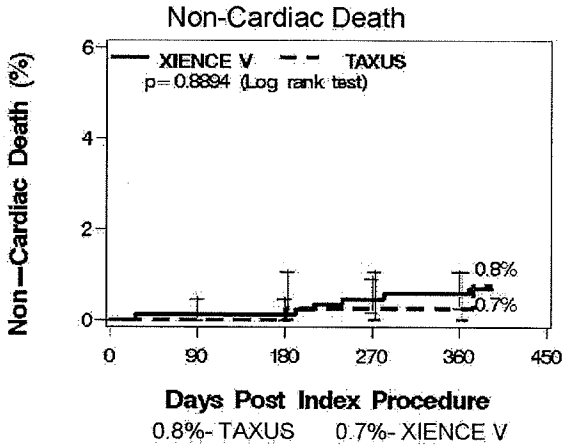
Figure 9.4-2: Kaplan Meier Hazard Curves for Time to Death through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

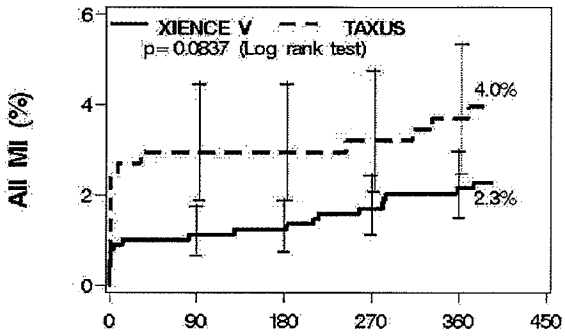


Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of MIs through 1 year are shown in Figure 9.4-3.

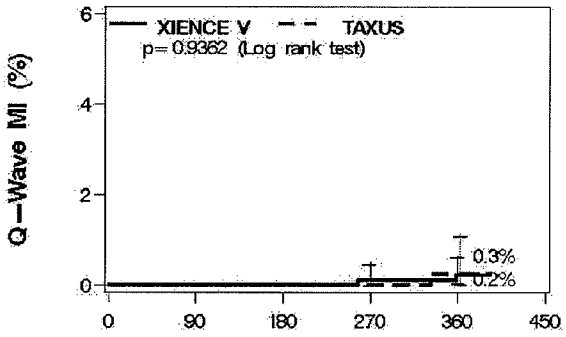
Figure 9.4-3: Kaplan Meier Hazard Curves for Time to First MI Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

All MI



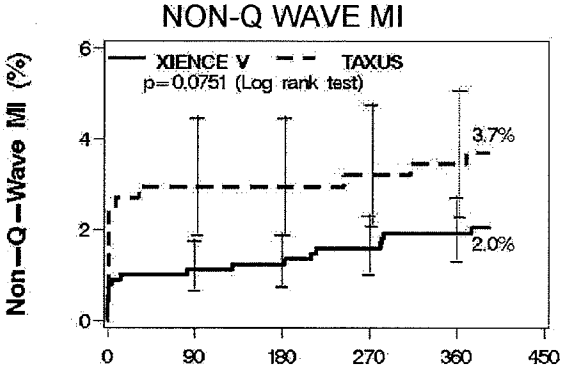
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Q-WAVE MI



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

NON-Q WAVE MI



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

9.4.1 Stent Thrombosis in SPIRIT II and SPIRIT III Pooled Analysis

The results for the pooled analysis rates of stent thrombosis at one year are shown below in Figure 9.4.1-1. Rates were low for both treatments in this pooled analysis and consistent with the published literature[10]. The rates of stent thrombosis were evaluated based on the SPIRIT II and III protocol defined definition and the ARC definition for definite + probable thrombosis (see definitions above in Section 8.2). These data are presented in table 9.4.1-1.

Table 9.4.1-1 Pooled Results for Stent Thrombosis through 1 year (SPIRIT II and SPIRIT III RCT)

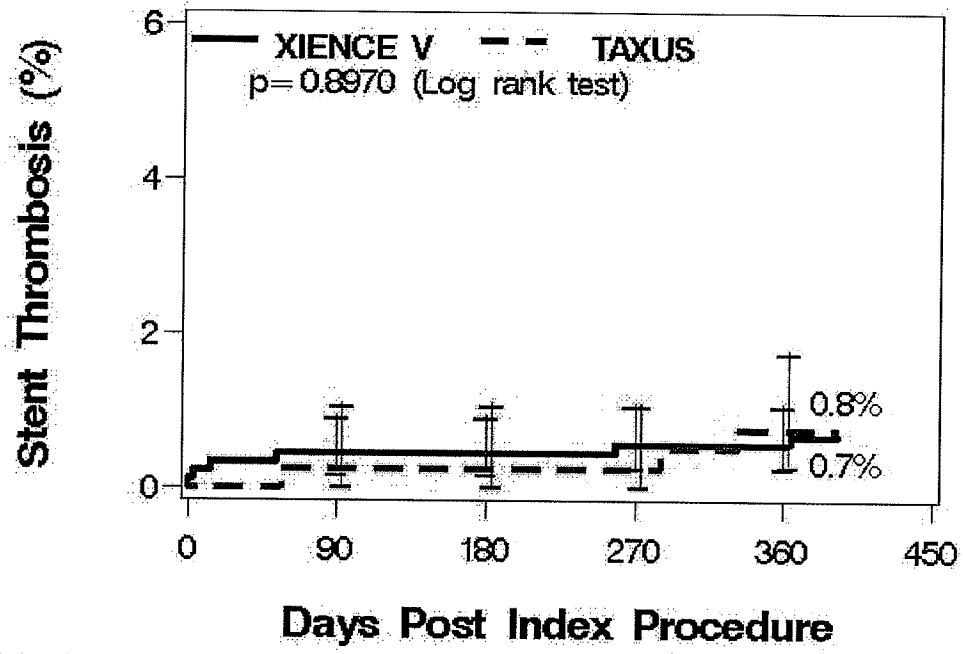
	XIENCE V (N=892)	95% CI[1]	TAXUS (N=410)	95% CI[1]
0 - 30 days				
Protocol	0.3% (3/890)	[0.07%, 0.98%]	0.0% (0/407)	[0.00%, 0.90%]
ARC (definite + probable)	0.4% (4/890)	[0.12%, 1.15%]	0.2% (1/407)	[0.01%, 1.36%]
31 days – 1 year				
Protocol	0.3% (3/866)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.3% (3/867)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
0 – 1 year				
Protocol	0.7% (6/867)	[0.25%, 1.50%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.8% (7/868)	[0.32%, 1.65%]	0.8% (3/394)	[0.16%, 2.21%]

Note: timeframe for 1 year includes the follow-up window (365 + 28 days).
[1] By Clopper-Pearson Exact Confidence Interval

[10] Ellis SG CA, Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol.* 2007;49:1043-1051.

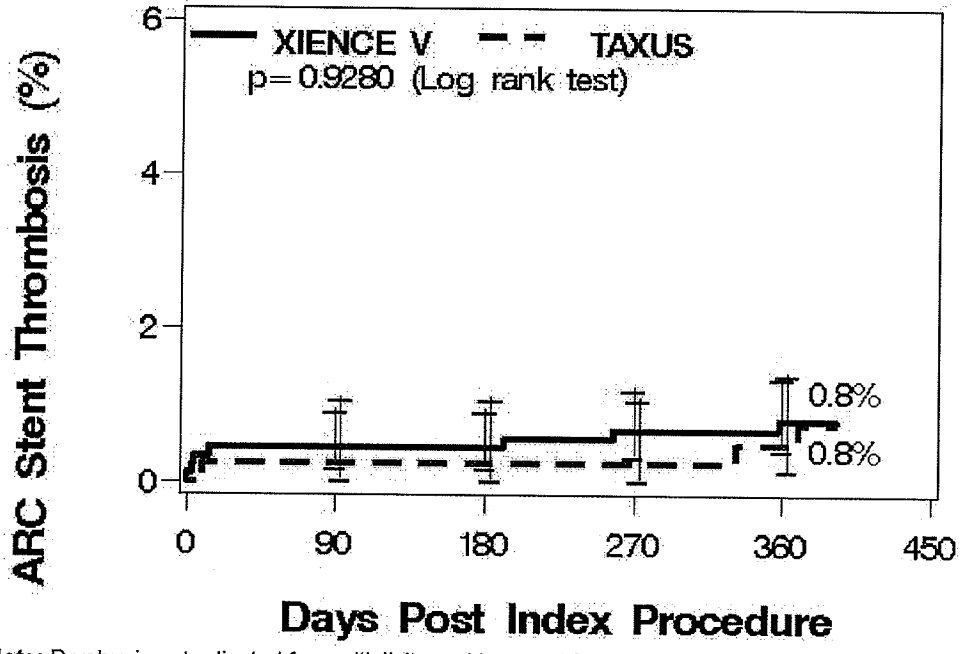
Figure 9.4.1-1: Kaplan Meier Hazard Curves for Time to First Stent Thrombosis Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

Protocol Defined Stent Thrombosis



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

ARC Defined Stent Thrombosis (Definite + Probable)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

9.4.2 Diabetics in SPIRIT II and SPIRIT III Pooled Analysis

Diabetic subjects comprise an important subject subgroup that is at increased risk for cardiovascular morbidity and mortality. Although diabetic subjects were included in the SPIRIT family of trials, there were no pre-specified hypotheses or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in diabetic individuals.

Table 9.4.2-1 shows the clinical outcomes through 1 year in subjects pooled from SPRIT II and III. The randomization was stratified by history of diabetes to assure a balance between the XIENCE V and TAXUS treatment arms. In XIENCE V patients, there were numerically higher event rates in diabetics compared with non-diabetics. The event rates for TAXUS in diabetics were lower than the event rates for TAXUS non-diabetics. Given the relatively small sample size of the diabetic population and potential for confounding variables, no conclusions can be drawn from these post-hoc analyses.

Table 9.4.2-1: Clinical Results in Diabetics and Non-Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

	Non-Diabetics XIENCE V (N=643)	Non-Diabetics TAXUS (N=296)	All Diabetics XIENCE V (N=249)	All Diabetics TAXUS (N=110)
TLR	2.5% (16/629)	7.6% (22/290)	4.5% (11/244)	1.0% (1/104)
TVR(CABG/PCI), non TL	2.5% (16/629)	4.1% (12/290)	3.3% (8/244)	2.9% (3/104)
All Death	1.0% (6/631)	2.4% (7/291)	2.0% (5/246)	0.0% (0/104)
Cardiac Death	0.3% (2/631)	1.4% (4/291)	1.2% (3/246)	0.0% (0/104)
Non-Cardiac Death	0.6%(4/631)	1.0%(3/291)	0.8%(2/246)	0.0% (0/104)
MI	1.4% (9/629)	4.5% (13/290)	4.5% (11/244)	2.9% (3/104)
Cardiac Death or MI	1.7% (11/629)	5.2% (15/290)	5.3% (13/244)	2.9% (3/104)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.0% (3/287)	1.3% (3/240)	0.0% (0/104)
ARC definite + probable	0.3% (2/627)	0.7% (2/287)	2.1% (5/241)	1.0% (1/104)

Table 9.4.2-2: Clinical Results in Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population – XIENCE V Subjects)

	Non-Diabetics (N=643)	All Diabetics (N=249)	Insulin-Dependent Diabetics (N=63)	Non-Insulin-Dependent Diabetics (N=186)
TLR	2.5% (16/629)	4.5% (11/244)	6.5% (4/62)	3.8% (7/182)
TVR(CABG/PCI), non TL	2.5% (16/629)	3.3% (8/244)	1.6% (1/62)	3.8% (7/182)
All Death	1.0% (6/631)	2.0% (5/246)	3.2% (2/63)	1.6% (3/183)
Cardiac Death	0.3% (2/631)	1.2% (3/246)	1.6% (1/63)	1.1% (2/183)
Non-Cardiac Death	0.6% (4/631)	0.8%(2/246)	1.6% (1/63)	0.5% (1/183)
MI	1.4% (9/629)	4.5% (11/244)	9.7% (6/62)	2.7% (5/182)
Cardiac Death or MI	1.7% (11/629)	5.3% (13/244)	9.7% (6/62)	3.8% (7/182)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.3% (3/240)	1.6% (1/61)	1.1% (2/179)
ARC definite + probable	0.3% (2/627)	2.1% (5/241)	1.6% (1/61)	2.2% (4/180)

9.4.3 Dual Vessel treatment in SPIRIT II and SPIRIT III Pooled Analysis

Subjects requiring treatment in more than one vessel comprise a subgroup that is at increased risk for cardiovascular events compared with single vessel disease patients. Although subjects requiring both single and dual vessel treatment were included in the SPIRIT family of trials,

there were no pre-specified hypothesis or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in dual vessel individuals.

Table 9.4.3-1 shows the clinical outcomes through 1 year in subjects pooled from SPRIT II and III. The randomization was stratified by the number of vessels treated to assure a balance between the XIENCE V and TAXUS treatment arms. Numerically lower event rates were observed for XIENCE V and TAXUS in single compared to dual vessel treatment. However, given the small sample size for dual vessel treatment, no conclusions can be drawn from this post-hoc analysis.

Table 9.4.3-1: Clinical Results in Single and Dual Vessel Treatment through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

	Single Vessel XIENCE V (N=752)	Single Vessel TAXUS (N=344)	Dual Vessel XIENCE V (N=140)	Dual Vessel TAXUS (N=65)
TLR	2.9% (21/735)	4.5% (15/333)	4.3% (6/138)	12.5% (8/64)
TVR(CABG/PCI), non TL	2.3% (17/735)	2.1% (7/333)	5.1% (7/138)	12.5% (8/64)
All Death	1.5% (11/739)	1.2% (4/333)	0.0% (0/138)	4.6% (3/65)
Cardiac Death	0.7% (5/739)	0.6% (2/333)	0.0% (0/138)	3.1% (2/65)
Non-Cardiac Death	0.8% (6/739)	0.6% (2/333)	0.0% (0/138)	1.5% (1/65)
MI	1.9% (14/735)	3.0% (10/333)	4.3% (6/138)	9.4% (6/64)
Cardiac Death or MI	2.4% (18/735)	3.3% (11/333)	4.3% (6/138)	10.9% (7/64)
Stent Thrombosis				
Protocol defined	0.3% (2/729)	0.6% (2/332)	2.9% (4/138)	1.6% (1/62)
ARC definite + probable (TLR not censored)	0.5% (4/730)	0.6% (2/332)	2.2% (3/138)	1.6% (1/62)

10.0 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before using the XIENCE V stent. Patient selection factors to be assessed should include a judgment regarding risk of long-term antiplatelet therapy. Stenting is generally avoided in those patients at a heightened risk of bleeding (e.g., patients with recently active gastritis or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

Antiplatelet drugs should be used in combination with the XIENCE V stent. Physicians should use information from the SPIRIT Clinical trials, coupled with current drug eluting stent (DES) literature and the specific needs of individual patients to determine the specific antiplatelet/anticoagulation regimen to be used for their patients in general practice. See also 5.2 – Precautions, Pre- and Post-Procedure Antiplatelet Regimen, Section 5.6 – Precautions, Use in Special Populations and Section 5.7 – Precautions, Lesion/Vessel Characteristics.

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

11.0 PATIENT COUNSELING AND PATIENT INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement.
- Discuss the risks associated with an everolimus-eluting stent.
- Discuss the risks of early discontinuation of the antiplatelet therapy.
- Discuss the risks of late stent thrombosis with DES use in higher risk patient subgroups.
- Discuss the risk/benefit issues for this particular patient.
- Discuss alteration to current life-style immediately following the procedure and over the long term.

The following patient materials are available for this product:

- A Patient Information Guide which includes information on coronary artery disease, the implant procedure and the XIENCE V Everolimus Eluting Coronary Stent System (provided to physician, on-line at www.XIENCEV.com/PatientGuide, or by calling customer service 1-800-227-9902).
- A Stent Implant Card that includes both patient information and stent implant information (provided in package)

12.0 HOW SUPPLIED

Sterile: This device is sterilized with ethylene oxide gas, non-pyrogenic. It is intended for single use only. Do not resterilize. Do not use if the package is opened or damaged.

Contents: One (1) XIENCE V Everolimus Eluting Coronary Stent System, one (1) Flushing tool, (for the XIENCE V EECSS Rapid Exchange (RX) Stent System), one (1) Stent Implant Card, one (1) Patient Information Guide.

Storage: Store in a dry, dark, cool place. Protect from light. Do not remove from carton until ready for use. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

13.0 OPERATOR'S INSTRUCTIONS

13.1 Inspection Prior to Use

- Carefully inspect the sterile package before opening and check for damage to the sterile barrier. Do not use if the integrity of the sterile package has been compromised.
- Do not use after the "Use By" date.
- Tear open the foil pouch and remove the inner pouch. **Note: the outside of the inner pouch is NOT sterile.** Open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
- Prior to using the XIENCE V Everolimus Eluting Coronary Stent System, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent does not extend beyond the radiopaque balloon markers. Do not

use if any defects are noted. However, **do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination or stent dislodgement from the delivery balloon.

Note: At any time during use of the XIENCE V Rapid Exchange (RX) EECSS, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

13.2 Materials Required

- Appropriate guiding catheter(s). See Table 1-1, XIENCE V Stent System Product Description
- 2 – 3 syringes (10 – 20 ml)
- 1,000 u/500 ml Heparinized Normal Saline (HepNS)
- 0.014 inch (0.36 mm) x 175 cm (minimum length) guide wire
- Rotating hemostatic valve with appropriate minimum inner diameter [0.096 inch (2.44 mm)]
- 60% contrast diluted 1:1 with heparinized normal saline
- Inflation device
- Pre-deployment dilatation catheter
- Three-way stopcock
- Torque device
- Guide wire introducer
- Appropriate arterial sheath
- Appropriate anticoagulation and antiplatelet drugs

13.3 Preparation

13.3.1 Packaging Removal

Note: The foil pouch is not a sterile barrier. The inner header bag (pouch) within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Rapid Exchange (RX) system, do not bend or kink the hypotube during removal.

2. Remove the product mandrel and protective stent sheath by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel and stent sheath removal, do not use this product and replace with another. Follow product returns procedure for the unused device.

13.3.2 Guide Wire Lumen Flush

1. Over the Wire (OTW) only: Flush the guide wire lumen with HepNS until fluid exits the distal end of the delivery system.

2. Rapid Exchange (RX) only: Flush the guide wire lumen with HepNS using the flushing tool supplied with the product. Insert the flushing tool into the tip of the catheter and flush until fluid exits the guide wire exit notch.

Note: Avoid manipulation of the stent while flushing the guide wire lumen, as this may disrupt the placement of the stent on the balloon.

13.3.3 Delivery System Preparation

1. Prepare an inflation device/syringe with diluted contrast medium.

2. Attach an inflation device/syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device/syringe.

3. With the tip down, orient the delivery system vertically.

4. Open the stopcock to delivery system; pull negative for 30 seconds; release to neutral for contrast fill.

5. Close the stopcock to the delivery system; purge the inflation device/syringe of all air.

6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.

7. If a syringe was used, attach a prepared inflation device to stopcock.

8. Open the stopcock to the delivery system.

9. Leave on neutral

Note: If air is seen in the shaft, repeat *Delivery System Preparation* steps 3 through 5 to prevent uneven stent expansion.

13.4 Delivery Procedure

1. Prepare the vascular access site according to standard practice.

2. **Pre-dilate the lesion with a PTCA catheter of appropriate length and diameter for the vessel/lesion to be treated.** Limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the XIENCE V Stent.

Note: The labeled stent diameter refers to expanded stent inner diameter.

3. Maintain neutral pressure on the inflation device attached to the delivery system. Open the rotating hemostatic valve as wide as possible.

4. Backload the delivery system onto the proximal portion of the guide wire while maintaining guide wire position across the target lesion.

5. Carefully advance the delivery system into the guiding catheter and over the guide wire to the target lesion. When using a Rapid Exchange (RX) system be sure to keep the hypotube straight. Ensure guiding catheter stability before advancing the stent system into the coronary artery.

Note: If unusual resistance is felt before the stent exits the guiding catheter, do not force passage. Resistance may indicate a problem and the use of excessive force may result in stent damage or dislodgement. Maintain guide wire placement across the lesion and remove the delivery system and guiding catheter as a single unit.

6. Advance the delivery system over the guide wire to the target lesion under direct fluoroscopic visualization. Utilize the radiopaque balloon markers to position the stent across the lesion. Perform angiography to confirm stent position. If the position of the stent is not optimal, it should be carefully repositioned or removed (see Section 5.14 – Precautions, Delivery System Removal). The balloon markers indicate both the stent edges and the balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion.

Note: Should **any resistance** be felt **at any time** during either lesion access or removal of the delivery system post-stent implantation, **remove the entire system as a single unit.** See Section 5.14 – Precautions, Delivery System Removal for specific delivery system removal instructions.

7. Tighten the rotating hemostatic valve. The stent is now ready to be deployed.

13.5 Deployment Procedure

CAUTION: Refer to Table 14-1: Typical XIENCE V Stent Compliance for *in vitro* stent inner diameter, nominal pressure, and RBP.

1. Prior to deployment, reconfirm the correct position of the stent relative to the target lesion using the radiopaque balloon markers.

2. Deploy the stent slowly by pressurizing the delivery system in 2 atm increments, every 5 seconds, until stent is completely expanded. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter ratio of about 1.1 times the reference vessel diameter (see Table 14-1). Maintain pressure for 30 seconds. If necessary, the delivery system can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall. **Do not exceed the labeled rated burst pressure (RBP) of 16 atm (1.62 MPa).**

3. Fully cover the entire lesion and balloon treated area (including dissections) with the XIENCE V stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion.

4. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to guiding catheter position.

5. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).

6. If the deployed stent size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is sub-optimal, the stent may be further expanded using a low profile, high pressure, non-compliant balloon dilatation catheter. If this is required, the stented segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the stent geometry. Deployed stents should not be left under-dilated.

CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
2.5 mm to 3.0 mm	**3.5 mm**
3.5 mm to 4.0 mm	**4.5 mm**

7. If more than one XIENCE V stent is needed to cover the lesion and balloon

treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents the balloon marker bands of the second XIENCE V stent should be positioned inside the deployed stent prior to expansion.

8. Reconfirm stent position and angiographic results. Repeat inflations until optimal stent deployment is achieved.

13.6 Removal Procedure

1. Deflate the balloon by pulling negative pressure on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position.

2. Fully open the rotating hemostatic valve.

3. While maintaining the guide wire position and negative pressure on the inflation device, withdraw the delivery system.

Note: Should **any resistance** be felt **at any time** during either lesion access or removal of the delivery system post-stent implantation, the entire system should be **removed as a single unit.** See Section 5.14 – Precautions, Delivery System Removal for specific delivery system removal instructions.

4. Tighten the rotating hemostatic valve.

5. Repeat angiography to assess the stented area. If post-dilatation is necessary, ensure that the final stent diameter matches the reference vessel diameter. **Assure that the stent is not under-dilated.**

13.7 Post-Deployment Dilatation of Stent Segments

1. All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to the vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guide wire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
2.5 mm to 3.0 mm	**3.5 mm**
3.5 mm to 4.0 mm	**4.5 mm**

14.0 *IN VITRO* COMPLIANCE INFORMATION

Table 14-1: Typical XIENCE V Stent Compliance
Nominal pressure for each diameter indicated by bold font.

Pressure		Stent ID (mm) by System Size				
(atm)	(MPa)	2.5 mm	2.75 mm	3.0 mm	3.5 mm	4.0 mm
8	0.81	**2.46**	**2.74**	2.90	3.46	3.86
9	0.91	2.52	2.81	**2.97**	**3.55**	**3.95**
10	1.01	2.58	2.87	3.04	3.63	4.03
11	1.11	2.63	2.92	3.10	3.69	4.10
12	1.22	2.68	2.97	3.15	3.75	4.17
13	1.32	2.72	3.01	3.19	3.80	4.23
14	1.42	2.75	3.05	3.23	3.84	4.28
15	1.52	2.78	3.08	3.26	3.89	4.33
16 (RBP)*	1.62	2.81	3.11	3.30	3.93	4.37
17	1.72	2.84	3.14	3.33	3.97	4.42
18	1.82	2.87	3.18	3.36	4.00	4.46

Note: These nominal data are based on *in vitro* testing at 37°C and do not take into account lesion resistance.
Ensure full deployment of the stent (see Section 13.5, Operator's Instructions, Deployment Procedure) and confirm the stent sizing angiographically.
*Do not exceed the rated burst pressure (RBP).

15.0 REUSE PRECAUTION STATEMENT

Do not use if sterile barrier is damaged. If damage is found call your Abbott Vascular, Cardiac Therapies representative.

For single patient use only. Do not reuse, reprocess or resterilize.

16.0 PATENTS

This product and/or its use are covered by one or more of the following United States patents: 5,040,548 ; 5,061,273 ; 5,154,725 ; 5,234,002 ; 5,242,396 ; 5,350,395 ; 5,451,233 ; 5,496,346 ; 5,514,154 ; 5,569,295 ; 5,603,721 ; 5,636,641 ; 5,649,952 ; 5,728,158 ; 5,735,893 ; 5,759,192 ; 5,780,807 ; 5,868,706 ; 6,056,776 ; 6,131,266 ; 6,179,810 ; 6,273,911 ; 6,309,412 ; 6,312,459 ; 6,369,355 ; 6,419,693 ; 6,432,133 ; 6,482,166 ; 6,485,511 ; 6,629,991 ; 6,629,994 ; 6,651,478 ; 6,656,220 ; 6,736,843 ; 6,746,423 ; 6,753,071 ; 6,818,247 ; 6,827,734 ; 6,887,219 ; 6,887,510 ; 6,890,318 ; 6,908,479 ; 6,921,411 ; 6,929,657 ; 6,939,373 ; 6,957,152. Other US patents pending. Foreign patents issued and pending.

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Graphical Symbols for Medical Device Labeling

Manufacturer	REF Catalogue Number	F French Size
Do not reuse, do not resterilize	STERILE EO Sterilized using Ethylene Oxide	Consult Instructions for Use
Use By	LOT Batch Code	Date of Manufacture
Guiding Catheter	PYROGEN Non-Pyrogenic	# Contents (Numeral represents quantity of units inside)
Inner Diameter		